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Evidence-Based Education • Practical Application

CLINICAL CHALLENGES:

- **What are the 4 dose phases in ketamine administration?**
- **How can ketamine emergence reactions be best managed?**
- **What are some emerging therapies for ketamine use in the ED?**

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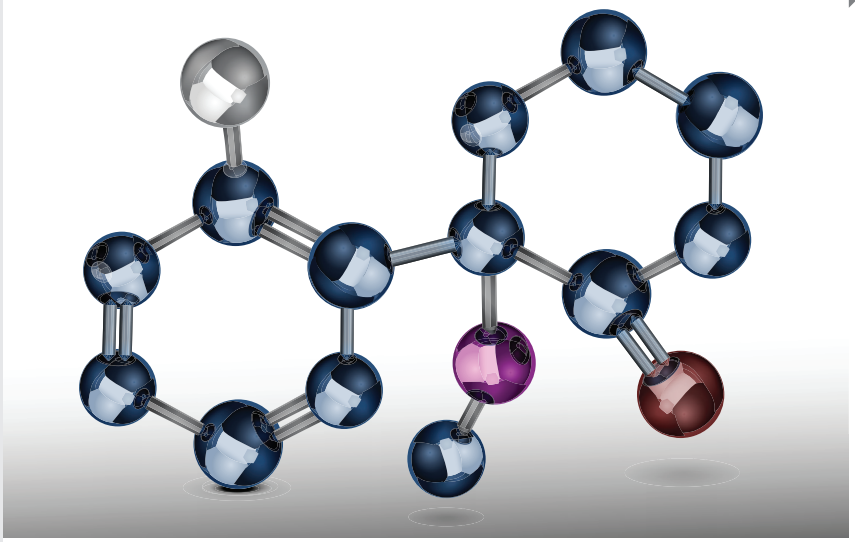

Current Concepts in Ketamine Therapy in the Emergency Department

Abstract

Ketamine has been in use since its development as a dissociative anesthetic in the 1960s, but it was largely confined to the operating theater or austere environments until used by emergency physicians to facilitate painful procedures in children. As the unique effects of ketamine across its dose-response curve were understood, new applications emerged. In low doses, ketamine has found an important role alongside or instead of opioids in the management of severe pain, and methods to slow its absorption allow higher, more effective doses while attenuating psychoperceptual effects. Ketamine's unique anesthetic properties have inspired its use as an induction agent for intubation without a paralytic and for the rapid, safe control of dangerously agitated patients. Emerging uses for ketamine in acute care include treatment for status epilepticus and alcohol withdrawal syndrome; however, its most important rising indication may be as an emergency treatment of depression and suicidality.

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Target Audience: This enduring material is designed for emergency medicine physicians, physician assistants, nurse practitioners, and residents.

Goals: Upon completion of this activity, you should be able to: (1) identify areas in practice that require modification to be consistent with current evidence in order to improve competence and performance; (2) develop strategies to accurately diagnose and treat both common and critical ED presentations; and (3) demonstrate informed medical decision-making based on the strongest clinical evidence.

CME Objectives: Upon completion of this activity, you should be able to: (1) apply the action of ketamine at its 4 dose phases (analgesic, recreational, partially dissociated, and fully dissociated) to its accepted uses in emergency care (analgesia, procedural sedation, and induction for rapid sequence intubation); (2) list common myths pertaining to the use of ketamine for traumatically injured patients; (3) describe strategies to minimize the likelihood of psychoperceptual effects when using ketamine for analgesia; and (4) explain how severe agitation can be safely managed using dissociative-dose ketamine.

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Case Presentations

CASE 1

A 43-year-old man presents to the ED after a trip and fall onto his outstretched hand…

- The patient's examination is notable for a dinner-fork deformity, and wrist radiograph shows a distal radius fracture with dorsal angulation.
- In order to reduce the fracture, procedural sedation with ketamine is performed. Though the usual dissociative dose of ketamine is ≥1 mg/kg IV, because you anticipated the procedure to be very brief, you chose a smaller dose of 40 mg.
- Shortly after administration, the patient begins screaming in terror and is obviously anguished by hallucinations and feelings of unreality. The clinical team is very concerned and looks to you for next steps…

CASE 2

A 22-year-old man presents after being thrown from his motorcycle; he was not wearing a helmet and has head injuries…

- Your primary survey demonstrates a low Glasgow Coma Scale score, failure to protect the airway, blood pressure of 77/40 mm Hg, and laxity on manual pelvic compression.
- Portable chest x-ray is unremarkable, but pelvic radiograph demonstrates an open-book pelvic fracture.
- You decide to intubate the patient for airway protection and presumptive need for operative management. Given the patient's hypotension, you call for 100 mg of rocuronium and 75 mg ketamine for rapid sequence intubation. Your colleague voices concern that ketamine is contraindicated in brain-injured patients…

CASE 3

A 74-year-old woman presents with hematemesis…

- The patient has a history of metastatic pancreatic cancer and has palliative goals of care; she does not wish to have any life-extending procedures done.
- She is in severe cancer-related pain, but is on high doses of opioids at home and describes a recent ED presentation in which staff was unable to control her pain with usual doses of opioids.
- The patient and her husband request that no tests or treatments be done beyond making her comfortable. She knows she has reached the end of her life and asks whether there is anything you can give her besides opioids to take away her pain…

Introduction

Ketamine was developed as an alternative to phencyclidine (PCP), the original dissociative anesthetic, which was synthesized in 1956. In a series of animal studies, PCP variably produced hyperkinetic frenzy and a cataplectic, trance-like state, and was then introduced to human patients undergoing surgery. Though PCP was effective in facilitating even the most painful surgical procedures by disconnecting the conscious brain from sensory stimuli, patients frequently suffered a severe and prolonged agitated delirium on emergence. In an effort to maintain the sensory deprivation effects of PCP without the turbulent recovery, a shorter-acting congener, ketamine, was synthesized in 1962.[1]

Ketamine acts on a range of receptor systems, but its primary mechanism of action is to inhibit glutamate transmission at central nervous system *N*-methyl-*D*-aspartate (NMDA) receptors, which are essential in the modulation of pain and other sensory processing, emotion, memory, and movement.[2] In sufficient doses, ketamine disconnects the mind without deactivating the mind, a state called *dissociation*. Unlike conventional sedatives, dissociation allows painful procedures to be performed without patient awareness, while airway, breathing, and circulatory tone are maintained. Ketamine was therefore originally confined to the surgical theater; however, its complex pharmacology has revealed layers of indications across varied domains over 60 years. It was soon determined that ketamine effected powerful analgesia in lower, consciousness-preserving doses; that dissociative-dose ketamine could be used to facilitate painful procedures in the emergency department (ED), on the battlefield, or in prehospital extrication scenarios; that it can be used to manage severe agitation and asthma; and most recently, ketamine has been demonstrated effective in treatment-resistant depression and suicidality.

This issue of *Emergency Medicine Practice* reviews ketamine's effects across its unusual dose-response curve, knowledge of which is essential when using ketamine for any purpose. Ketamine's established indications in emergency medicine (eg, procedural sedation, rapid sequence intubation [RSI], and analgesia) are reviewed, focusing on recent de-

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velopments and areas of disagreement. Controversial indications, including alternatives to RSI (eg, delayed sequence intubation and ketamine-only breathing intubation), and the use of ketamine in the treatment of agitation, management of severe asthma, and adjunctive treatment of status epilepticus and alcohol withdrawal syndrome are examined. Ketamine's emerging role as a treatment of depression and suicidality and management of chronic pain and substance use disorders will also be reviewed.

The Ketamine-Brain Continuum

Most medications have a conventional dose-response curve, where administering higher doses of the drug produces more of the same effect. For example, 5 mg intravenous (IV) morphine produces modest analgesia, 10 mg produces more analgesia, and 15 mg more analgesia still. With most agents, adverse effects predictably follow the same curve, ie, the higher the morphine dose, the more likely respiratory depression will be. Ketamine's actions and complications follow a different pattern, where escalating doses produce qualitatively different desired and undesired effects.[3,4]

Ketamine dosage/effects fall into 4 loosely defined ranges: (1) analgesic dose, (2) recreational dose, (3) partially dissociated dose, and (4) dissociated dose. The continuum of this dosage/effect is represented in **Figure 1**.

The described stages of the ketamine dose-response curve have overlapping dose ranges that are variable among patients. At a small analgesic dose (<0.1 mg/kg IV) or a large dissociative dose (>2 mg/kg IV), the effects are consistent; however, the effect of intermediate doses is unpredictable. A feature of ketamine's pharmacodynamics that accounts for its remarkable margin of safety[5] is the *dissociation threshold*, above which higher doses do not produce further effect. A dissociated patient does not become more dissociated with more ketamine; higher doses only prolong the duration of action.

Analgesic Dose (0.1-0.3 mg/kg IV)[6]

At low doses, ketamine has no effect on consciousness, minimal effect on perception or emotion, but is a powerful analgesic.[6]

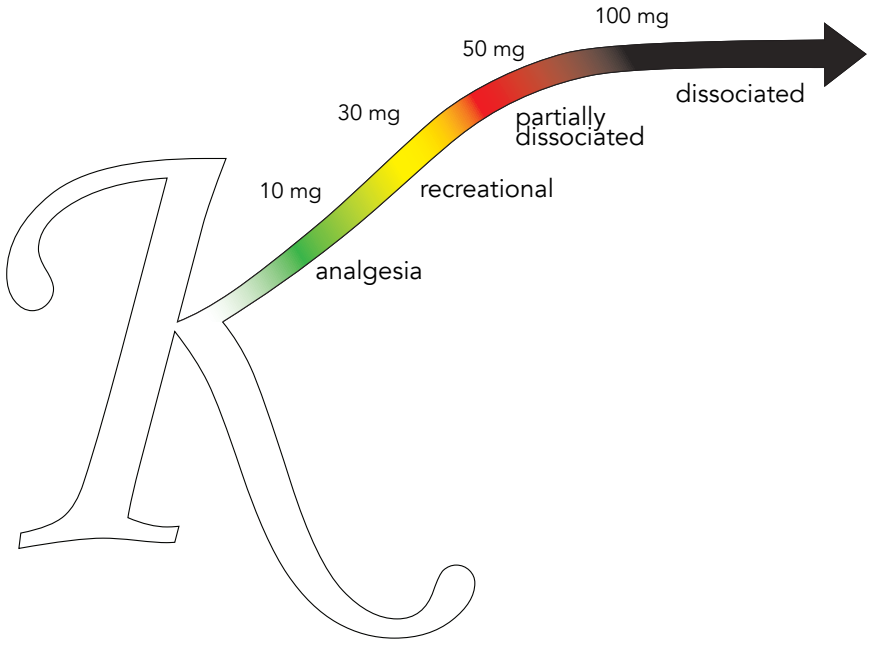
Recreational Dose (0.2-0.5 mg/kg IV)

As analgesic dosing escalates, analgesia becomes more profound but ketamine's psychoperceptual effects supervene. The patient's level of consciousness is undiminished, but visual, auditory, and emotional fields are distorted in the manner of hallucination or derealization. Many patients—especially if properly coached prior to ketamine administration—will find these sensations odd or enjoyable; in fact, ketamine is widely used as a recreational drug for this purpose. However, some patients will experience perceptual disturbances as unpleasant, anxiety-producing, or distressing. Psychoperceptual effects can be interpreted and reported as dizziness, fear, loss of control, or feeling "stoned." Though important bodily functions are unaffected in the recreational dose range, some patients will experience significant psychiatric distress. Because awareness and consciousness are preserved, psychiatric distress can usually be alleviated with reassurance that all is well and that they are experiencing a drug effect that will wear off soon, though treatment with a sedating medication is sometimes worthwhile.

Partially Dissociated Dose (0.4-0.8 mg/kg IV)

Partial dissociation occurs when the ketamine dose is insufficient to effect full dissociation but causes consciousness to be impaired and incompletely disconnected from external stimuli. Partially dissociated patients may lose the ability to see, hear, feel pain, speak, or move; these capabilities may fade in and out. Patients can experience profound derealization and

Figure 1. The Ketamine Dosage/Effects Continuum (for 70-kg Adult)



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loss of control of their interface with the world and their own identity. Nonetheless, in partial dissociation, some degree of awareness is maintained, so patients are cognizant of the severe disruption in their sensory, emotional, and ontological landscape. Though this experience, colloquially referred to as a *K-hole*, can be perceived positively as a mystical voyage, many will react with terror that will manifest either explicitly or—if the patient is unable to speak—silently, as severe psychiatric distress. Patients in partial dissociation may become incoherently panicked and violently agitated as if trapped in a nightmare, which they are. The analgesic, recreational, and partially dissociated phases can be bypassed with a sufficient IV bolus dose of ketamine; however, the patient cannot be prevented from passing back through partial dissociation as that dose is metabolized and the patient emerges. These distressing episodes of psychiatric distress in partial dissociation, which can be severe enough to cause clinicians to exclude ketamine from their therapeutic armamentarium, are called *emergence reactions*.

Dissociative Dose (≥1mg/kg IV)[7]

In full dissociation, patients are isolated from all external stimuli, which is the desired state in most cases in which ketamine is used to facilitate a painful procedure or endotracheal intubation. A dissociated patient perceives no sights, sounds, or pain, and cannot interact. Though nystagmus, random, and reflexive movements are common, dissociated patients are incapable of volitional action. Unlike with conventional sedatives, the brain is activated, patients are awake, cardiorespiratory function is preserved or stimulated, but the dissociated brain is unaware of the reality of what is happening around them. Dissociated patients are awake, but unconscious.

Though airway, breathing, and circulation in subdissociation are altered only by the patient's emotional state (eg, psychiatric distress will cause hypertension and tachycardia), dissociation has important hemodynamic consequences, described in the "Procedural Sedation," section on page 6. All patients dissociated for any indication who are not intubated require continuous cardiorespiratory monitoring, with an airway-capable clinician immediately available, for the duration of dissociation.

Analgesia

Ketamine is a powerfully effective and extremely safe analgesic agent. When used in analgesic dose (0.1-0.3 mg/kg IV), ketamine will relieve pain of any etiology or severity, without concern for hemodynamic adverse effects. ED use of ketamine for analgesia without the need for cardiorespiratory monitoring is supported by a robust base of prospective studies and society guidelines. Ketamine is often considered an opioid alternative in the management of moderate or severe pain, and though it may be properly used as a first-line analgesic agent, the majority of available supporting literature for its use is when opioids are undesired or ineffective.[8-11]

Unlike opioids, analgesic-dose ketamine does not carry the risk for respiratory depression or hypotension. Compared to equipotent dosing of opioids, ketamine causes less nausea, no constipation, and is not histaminergic. An adverse effect associated with analgesic-dose ketamine is psychoperceptual disturbance which, when bothersome to the patient, can be easily attenuated using several strategies. Anticipatory guidance and reassurance are often effective at framing sensory changes that occur as analgesic dosing slides into recreational range, with distraction from pain being a "feature, not a bug." As with other hallucinogens, set and setting strongly affect one's emotional response, and if a patient being treated with ketamine expects mild hallucinations and is roomed in a quiet area or provided headphones for music, an unpleasant experience is less likely.[12]

Dosing and Administration for Analgesia

The most common dosing strategy for using ketamine for analgesia is IV push, though bolus-dose recommendations vary from 0.1 to 0.3 mg/kg. The wide analgesic dosing range reflects ketamine's unconventional dose-response. At 0.1 mg/kg IV, bothersome psychoperceptual effects are very unlikely, but analgesia may be inadequate, whereas an IV dose of 0.3 mg/kg will usually be effective for pain but may constitute a dose where patients may become anxious or dysphoric.

Although emergency clinicians often favor drugs with rapid onset and offset, ketamine, when used for pain, benefits from slow delivery because analgesic efficacy corresponds to total dose, while psychoperceptual effects are accentuated by rapid administration. Therefore, desired effects are augmented and undesired effects are diminished by slow administration.[6,13] This is easily accomplished by infusing ketamine over 10 to 15 minutes (by diluting in 50 or 100 mL saline), which lessens psychoperceptual effects and allows for a larger dose. IV ketamine is relatively short-acting; therefore, for patients expected to have prolonged moderate or severe pain (eg, polytrauma), a dose of 0.3 mg/kg over 15 minutes followed by a continuous infusion at 0.3 mg/kg/hr is reliably effective and well-tolerated. Once the continuous infusion is underway, titrate by 25% increments up or down to augment analgesia or ameliorate sensory disturbances as needed.

Ketamine may be administered by a variety of alternative routes that both abridge the need for IV access and provide favorable pharmacokinetics by slowing onset and prolonging duration of action.

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- Analgesic-dose ketamine delivered by intranasal atomization is well-studied in adult and pediatric randomized controlled trials and is effective at a dose of 0.5 to 1.5 mg/kg intranasal, with 1 mg/kg often recommended.[14-19]
- One randomized controlled trial and several case series show that ketamine is effectively administered via breath-actuated nebulization at 0.75 to 1.5 mg/kg, which carries the additional benefit of allowing patient-controlled analgesia.[20-24]
- IM administration of ketamine for analgesia at a dose of 0.5 mg/kg is effective and has been used extensively in military applications.[25,26]
- A small literature base demonstrated that oral ketamine is effective and safe for pain (and, at higher doses, sedation), with a wide dose range, from 0.5 mg/kg to 5 mg/kg.[27-32] For oral administration, the injectable preparation is used and may be diluted in a beverage to mask the taste. Though ketamine's lack of titratability makes navigating the narrow therapeutic window between effective pain and bothersome psychoperceptual effects more challenging, the benefits of oral administration make this approach deserving of further study.

Ketamine is effective as analgesic monotherapy or in combination with opioids,[33-37] nitrous oxide,[38] or simple analgesics. As with procedural sedation, co-administration of conventional sedatives (benzodiazepines or antipsychotics) will effectively prevent and treat ketamine-related psychiatric discomfort. Butyrophenone neuroleptics (haloperidol, droperidol) have analgesic effects,[39-41] and patients treated with these agents are more likely to respond well to subsequent ketamine analgesia, if needed, in addition to frequently experiencing significant pain relief as well as sedation.[42] This strategy may be useful when managing patients with chronic opioid use, chronic pain, or in palliative care, for which retrospective studies and case reports demonstrate that ketamine has particular utility.[43-46]

Procedural Sedation

Emergency clinicians commonly perform painful procedures that require analgesia, anxiolysis, and/or amnesia in order to be completed effectively and humanely. Children and patients who are developmentally delayed or otherwise uncooperative may also require sedation in order to complete radiology studies and other components of the workup. The use of centrally acting medications to facilitate painful or painless procedures is often called *conscious sedation*; however, this term is synonymous with *moderate sedation*, which corresponds to a depth of anesthesia in which the patient responds purposefully to verbal commands or light tactile stimulation. Because moderate sedation is inadequate for many ED-based procedures (such as reducing a fractured wrist or draining an abscess), and because dissociation does not fit within the conventional sedation continuum, where deeper planes of anesthesia correspond to loss of critical bodily functions such as airway reflexes and respiratory drive, the preferred term is *procedural sedation*.[47] Procedural sedation encompasses the entire sedation continuum: minimal, moderate, and deep sedation; general anesthesia; and dissociation. A robust body of evidence supports the use of a variety of anesthetic agents by emergency clinicians that will safely and effectively sedate patients as lightly or as deeply as needed to perform procedural sedation across the range of ED procedures.[48,49]

Ketamine's principal advantage over alternative procedural sedation agents is that fully dissociated patients are impervious to and amnestic of painful stimuli of any magnitude, while airway, breathing, and circulatory tone are usually maintained. Facilitating exquisitely painful procedures with opioids or conventional sedatives (eg, propofol or midazolam) may require doses that cause respiratory depression, loss of airway reflexes, or hypotension. Though emergency clinicians are able to support these vital functions during a period of deep sedation, dissociation with ketamine is frequently preferable because, in most cases, breathing continues, blood pressure is augmented by ketamine's weakly catecholaminergic effect, and airway reflexes, including swallowing, are preserved.

Dosing and Administration for Procedural Sedation

Ketamine carries the additional benefit of being reliably effective by intramuscular (IM) administration. This is a particular advantage in children, when placing an IV cannula is more likely to be difficult and poorly tolerated. Although many clinicians request vascular access prior to ketamine procedural sedation, prospective data demonstrate that this is not necessary.[50] An intermediate strategy is to dose ketamine IM and place a line after the patient has dissociated. Ketamine is less potent when administered IM; the dissociative dose is 3 to 4 mg/kg IM compared to 1 to 2 mg/kg IV.[7]

Ketamine has been used as a procedural sedation agent in children for decades but was avoided in adults for fear of psychiatric distress. Emergence phenomena occur less frequently in children, in part because developing brains are more accepting of distortions of perception and reality. More recently, the use of ketamine for procedural sedation and analgesia in adults has become widespread,[51] and a variety of techniques have been developed to mitigate ketamine's adverse effects.

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Managing Adverse Effects

Psychiatric distress can be effectively prevented, anticipated, and treated.[52] The emotional valence of a ketamine anesthetic depends on the patient's expectations and mood prior to induction; distressing emergence reactions are less likely if anxiety and pain are treated with preprocedural coaching and analgesia. The patient should be allowed to emerge in a quiet or music-enhanced environment, if possible, and psychiatric distress can be anticipated by monitoring facial expressions and vital signs.[12] If distress occurs, it should be treated immediately with a conventional sedative such as propofol or midazolam. Psychiatric distress at the time of induction indicates that the patient is in partial dissociation due to an inadequate dose of ketamine; in this case, the treatment is to push the patient to full dissociation with an additional ketamine dose.

Hypertension and tachycardia occur reliably during dissociation; this is usually mild, transient, and of no consequence. However, patients with cardiovascular fragility (such as decompensated congestive heart failure) may not tolerate a sudden increase in afterload and myocardial oxygen demand,[53] and in these cases it is prudent to use an alternative agent or assiduously treat hyperdynamic vital signs. Propofol is well suited for this purpose, as it is both a sympatholytic and vasodilator.

Some dissociated patients will develop muscle rigidity or hypertonicity that interferes with orthopedic procedures; this is readily abolished with midazolam or propofol.[54] Postprocedural nausea and vomiting is common and responds to usual antiemetics. Administering ondansetron prophylactically prior to ketamine is effective but unnecessary.[55] Hypersalivation is common, especially in children, and is usually easily managed expectantly or with gentle suction; prophylactic anticholinergic treatment is not recommended.[7]

Ketamine is favored in many ED-based procedural sedation cases because dissociated patients are unaffected by painful stimuli as they generally continue to breathe and manage secretions normally. Nonetheless, dangerous hypoventilation can and does occur in dissociation from a variety of mechanisms, including laryngospasm. Vigilant cardiorespiratory monitoring must therefore be maintained throughout (see the "Treatment of Agitation" section on page 10).

Ketamine, Propofol, and Dexmedetomidine

Because propofol effectively mitigates many of ketamine's adverse effects, some clinicians administer propofol with ketamine ("ketofol").[56,57] In initial studies, this was done by mixing the 2 agents into the same syringe in a 1:1 ratio; however, the differing pharmacokinetic profiles of the 2 agents suggest this is not necessary, and common practice now is to administer these in separate syringes, allowing for repeat doses of either as needed, depending on desired outcome. Randomized controlled trials demonstrate that ketofol is safe and effective but is not superior to ketamine monotherapy.[58,59] Because of their divergent half-lives, when co-administered, propofol effects dominate in short procedures and ketamine in longer procedures. It may be preferable to favor induction with a usual dissociative dose of ketamine, with propofol ready to administer in small aliquots to treat adverse effects when they arise.[60,61]

Dexmedetomidine has many of the properties that make propofol a useful adjunct to ketamine procedural sedation, with better-aligned pharmacokinetics and reduced incidence of respiratory depression. A modest evidentiary base, including randomized trial data, suggests that "ketadex"(ketamine and dexmedetomidine) may effectively harness ketamine's advantages while minimizing its adverse effects.[62-65]

Rapid Sequence Intubation

RSI, the near-simultaneous administration of an induction agent and a paralytic, is the strategy used to facilitate the vast majority of endotracheal intubation procedures in the ED.[66] In the United States, the most commonly used induction agent is etomidate, followed distantly by ketamine and propofol.[67] Ketamine offers similar advantages in RSI to its use in procedural sedation, without the concerns around psychiatric distress, as RSI patients are intubated and (hopefully) deeply sedated following intubation.

Unlike etomidate or propofol, ketamine provides analgesia that outlasts its effect as an anesthetic. When administered in sufficient doses, ketamine also has a longer duration of action than etomidate or propofol, a decided advantage in the ED.[68,69] Dissociative-dose ketamine has a very wide therapeutic window. Because multiple ketamine concentrations are often available in the same department, there are described cases of 10-fold or even 100-fold accidental overdoses that resolved without lasting consequence.[5]

Large registry and retrospective cohort studies are mixed regarding whether higher doses of ketamine are more likely to cause hypotension, with the balance suggesting that higher doses do not cause hypotension, though lowering the dose of any induction agent in patients at risk for hypotension is a consideration that should be balanced against the risk for potential undersedation.[70-74] One reasonable strategy to manage this divergent guidance is to base ketamine dosing in hypotensive patients on their wakefulness: if the patient is perfused enough to be awake, err on the side of administering a full dissociative dose. If hypoperfusion is severe enough to significantly impair the level of consciousness, a smaller induction dose (0.5 mg/kg) may be reasonable.

Often-cited contraindications to ketamine for RSI, which include increased intracranial pres-

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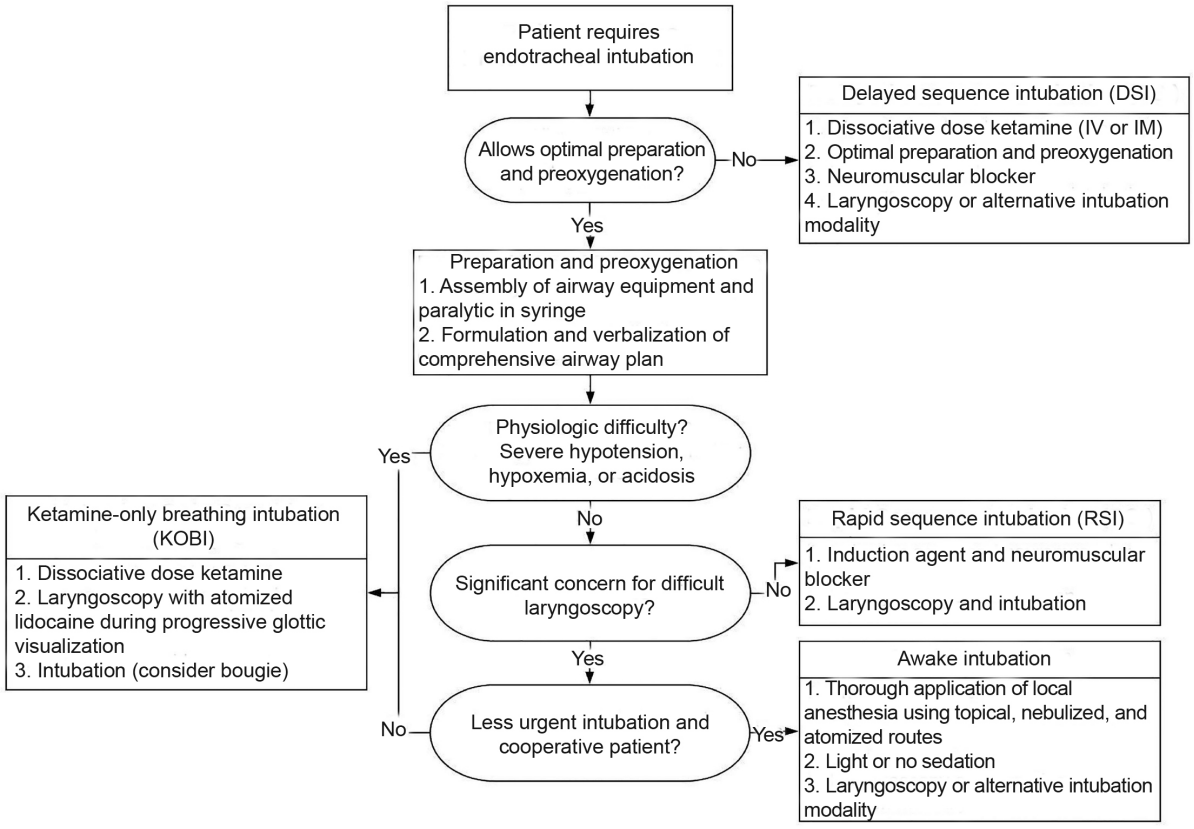
sure, increased intraocular pressure, and psychiatric disease, have been debunked.[74-77] Due to its catecholaminergic effect, ketamine should be avoided in patients in whom an increase in heart rate or blood pressure is undesirable, such as aortic dissection, subarachnoid hemorrhage, hypertensive pulmonary edema, or myocardial ischemia. For patients with or at risk for hypotension, data are mixed on the relative merits of ketamine and etomidate;[78-83] however, etomidate causes adrenal suppression. Though the clinical significance of etomidate-related adrenal suppression remains controversial,[84,85] clinicians can avoid this deliberation by choosing ketamine. Ketamine is a weak bronchodilator and is the induction agent of choice for most patients being intubating for reactive airway disease.[86]

Alternatives to Rapid Sequence Intubation

Ketamine offers a variety of advantages over alternative induction agents when administered simultaneously with a paralytic during RSI. However, RSI itself entails several critical risks. Patients with anatomic difficulty may be challenging or impossible to intubate by laryngoscopy. If endotracheal intubation and subsequent attempts to re-establish ventilation and oxygenation fail, dangerous hypoxia supervenes. Patients with oxygenation or ventilation deficit may not be able to sustain even a brief period of apnea without developing critical hypoxemia or acidemia. Patients with perfusion deficit are so hemodynamically tenuous that the abrupt transition from positive to negative pressure ventilation during RSI may precipitate cardiovascular collapse. These risks are exacerbated if the patient is too agitated to allow adequate preoxygenation and preparation, and performing RSI before these steps are undertaken is particularly dangerous. Because ketamine dissociation causes unconsciousness and the capacity to tolerate laryngoscopy as airway, breathing, and circulatory tone are maintained, 2 ketamine-based alternatives to RSI have been developed to address its limitations that may be decisive in the small but especially vulnerable subset of critically ill patients requiring emergency airway management: ketamine-only breathing intubation (KOBI) and delayed sequence intubation (DSI). The relationship between these procedures is represented in **Figure 2.**

Figure 2. Relationship Between Rapid Sequence Intubation, Delayed Sequence Intubation, and Ketamine-Only Breathing Intubation


Patient requires endotracheal intubation
Allows optimal preparation and preoxygenation?
No
Delayed sequence intubation (DSI)
1. Dissociative dose ketamine (IV or IM)
2. Optimal preparation and preoxygenation
3. Neuromuscular blocker
4. Laryngoscopy or alternative intubation modality
Yes
Preparation and preoxygenation
1. Assembly of airway equipment and paralytic in syringe
2. Formulation and verbalization of comprehensive airway plan
Physiologic difficulty? Severe hypotension, hypoxemia, or acidosis
Yes
No
Ketamine-only breathing intubation (KOBI)
1. Dissociative dose ketamine
2. Laryngoscopy with atomized lidocaine during progressive glottic visualization
3. Intubation (consider bougie)
Significant concern for difficult laryngoscopy?
No
Rapid sequence intubation (RSI)
1. Induction agent and neuromuscular blocker
2. Laryngoscopy and intubation
Yes
No
Less urgent intubation and cooperative patient?
Yes
Awake intubation
1. Thorough application of local anesthesia using topical, nebulized, and atomized routes
2. Light or no sedation
3. Laryngoscopy or alternative intubation modality

Source: Alternatives to rapid sequence intubation: contemporary airway management with ketamine. Andrew H. Merelman, Michael C. Perlmutter, Reuben J. Strayer. *Western Journal of Emergency Medicine*. Volume 20, Issue 3. Pages 466-471. Reprinted by Creative Commons Attribution (CC BY 4.0) License

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Delayed Sequence Intubation

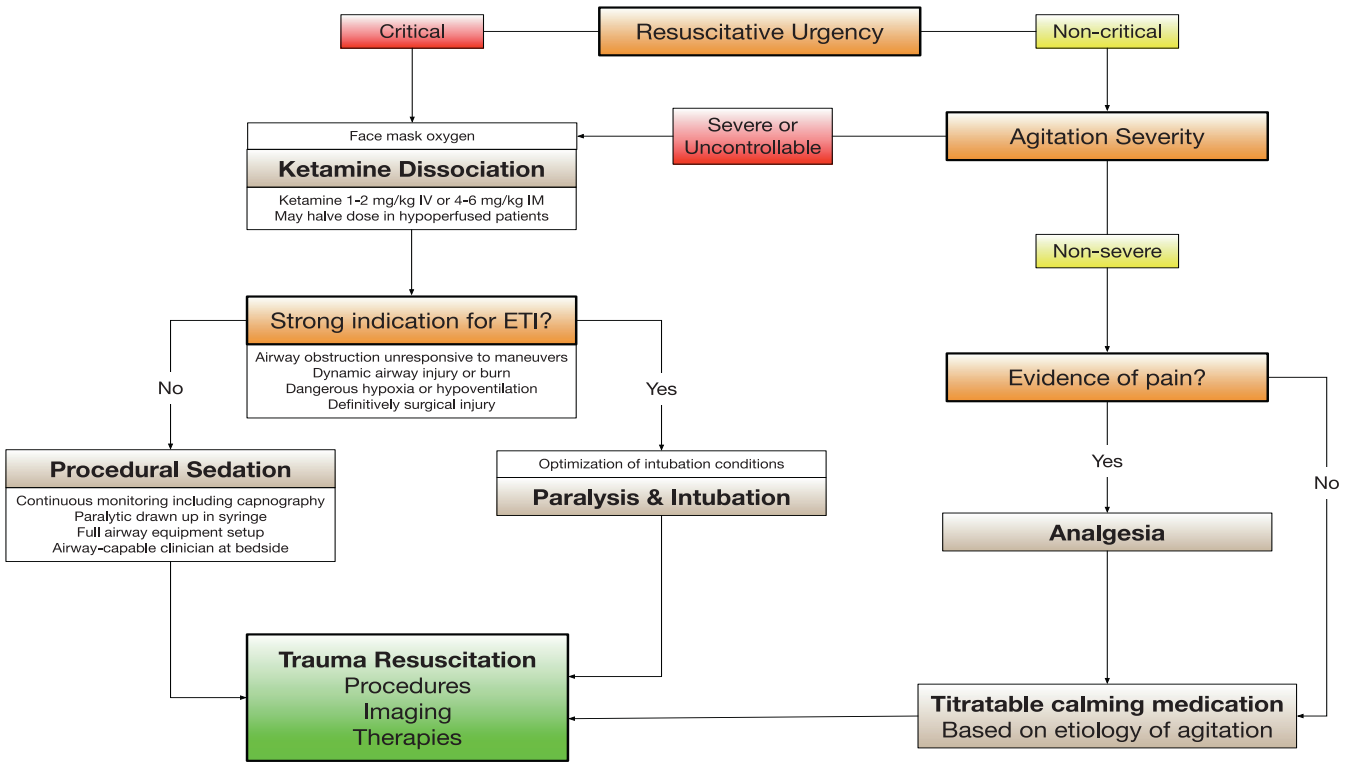
DSI is an airway pharmacology strategy to address patient agitation that may impair preoxygenation and procedural preparation. Typical scenarios include the hypoxic patient ripping off their face mask and the dangerously injured patient who will not allow a trauma evaluation. DSI uses a dissociative dose of ketamine to effect unconsciousness, after which critical steps in preparation for intubation (eg, application of high-flow oxygen, establishment of vascular access, supportive therapies, or initial treatment of the underlying condition) and gathering of supplies can be undertaken. Once preparation and preoxygenation have progressed sufficiently, the usual dose of a paralytic is administered, and laryngoscopy proceeds as in RSI. DSI has a small body of supporting evidence,[87-89] including a 2023 randomized controlled trial in trauma patients,[90] demonstrating improved oxygenation and first-pass success. As with KOBI and procedural sedation, dissociation is ideally effected gradually rather than as a single, quick IV bolus, using either administration as IV piggyback over several minutes or small, frequent aliquots (eg, 25 mg every 20 seconds).

Some patients managed with DSI, once they have been stilled by dissociation and properly treated, will not require intubation. The most common example is the respiratory distress patient who does not tolerate noninvasive ventilation for agitation, but once dissociated and effectively treated, clinically improves. Clinicians should, nonetheless, prepare for intubation, including ready access to paralysis, and monitor very closely until dissociation has resolved and the patient's trajectory is clear.[91] This intubation-sparing feature of DSI can be applied in the management of agitated polytrauma patients who otherwise are often promptly intubated to facilitate their initial evaluation and imaging, as presented in **Figure 3.**

Ketamine-Only Breathing Intubation

KOBI is the use of dissociative-dose ketamine without a paralytic to facilitate endotracheal intubation in patients at high risk to be harmed by paralysis. The strategy commonly used in this situation by anesthesiologists is topicalized awake tracheal intubation, which relies on dense application of local anesthesia and minimal to no sedation, usually using a flexible endoscope, so that intubation can be carried out with safety on a patient who is not only continuing to breathe but is, in fact, awake. The availability of single-use disposable endoscopes addresses an important barrier to ED-performed awake intubation; however, many emergency clinicians do not feel comfortable performing flexible endoscopy, and patients being intubated in the ED are often not cooperative enough to participate in a traditional

Figure 3. Agitation Management in the Trauma Patient



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awake technique. KOBI is an emerging approach with a small, low-level evidence base[92-95] that offers some of the safety benefit of awake tracheal intubation while overcoming the barriers that limit the use of topicalized awake technique in emergency medicine. Performing endotracheal intubation with ketamine monotherapy is alternatively called *ketamine-assisted intubation, ketamine-facilitated intubation, ketamine-only intubation, ketamine-supported intubation,* and *dissociated awake intubation*. It does not have a conclusive record of safety, as does RSI, and should be reserved for cases where RSI is judged to be particularly dangerous.[96-99]

KOBI is performed by administering a dissociative dose of ketamine, ideally delivered IV over 1 to 2 minutes, to avoid the transient period of apnea that sometimes occurs with quick IV administration. When the patient dissociates, laryngoscopy (or flexible endoscopy) and tube delivery may proceed as usual, with several caveats. Administering 4% lidocaine directly to the posterior oropharynx and glottis is recommended to attenuate gagging, coughing, and other airway reflexes that may interfere with the procedure. If time and cooperation allow, this may be performed prior to induction using a purpose-built atomization device; otherwise, application as laryngoscopy proceeds with deliberate slowness will usually produce satisfactory conditions. Clinicians accustomed to RSI must anticipate more difficult laryngeal exposure and tube delivery,[100] which may be addressed through the use of video laryngoscopy and a bougie. Most importantly, dissociated patients may develop jaw rigidity or laryngospasm, and any nonparalyzed patient being intubated is at risk for emesis. KOBI should always be undertaken with a paralytic drawn up in syringe at bedside, as well as at least one ready for suction.

Treatment of Agitation

Agitation is one of the cardinal presentations in emergency and prehospital medicine. For years, the mainstay of treatment was one-size-fits-all "5 and 2," that is, 5 mg of haloperidol and 2 mg of lorazepam, mixed in the same syringe and administered IM or IV. Agitation treatment paradigms have matured in recent years; for mild agitation, treatments are tailored to its underlying cause, whereas moderately agitated patients may be disruptive, and treatment relies on agents with more favorable pharmacokinetics, such as droperidol and midazolam.[101]

What defines "severe" agitation is the presence of *danger*. Danger arises from agitation in 2 ways: Patients may be uncontrollably violent, meaning that they cannot be subdued with available resources and represent an immediate threat to themselves and others from the agitation itself. The second type of dangerous agitation occurs when an agitated patient is thought to be harboring a dangerous condition and the agitation, while not itself an immediate threat, prevents the clinical team from diagnosing or treating the underlying dangerous condition, such as head injury, hyperthermia, or hypoglycemia.

Because ketamine is not titratable above analgesic doses, and because dissociated patients require resuscitation-level support, ketamine is not an appropriate agent to treat routine, moderate agitation. Patients who manifest severe, dangerous agitation are critically ill and require critical care resources; agitation in these cases is optimally treated with ketamine.[102] Patients whose agitation does not pose a dangerous threat should be treated with a conventional, titratable sedative, usually monotherapy or combination therapy with an antipsychotic and/or benzodiazepine. A useful heuristic when considering ketamine to treat agitation is to consider whether intubating the patient would be a reasonable outcome; if that intensity of care is unwarranted by the patient's present condition, alternative calming agents are likely preferred.

Dosing and Administration for Agitation

Because moderate agitation poses no danger, treatment emphasizes medication safety, and clinicians err to under-treatment, recognizing that a second dose or alternative agent may be needed. Severe agitation requires a different approach that accounts for the urgency to establish immediate control of the patient in order to address the danger posed by uncontrollable violence or underlying dangerous conditions. This approach starts with assembling adequate personnel to approach the patient, applying oxygen, and relieving dangerous restraint holds, but centers on treating agitation with dissociative-dose IM ketamine.

Ketamine has excellent pharmacokinetics by the IM route and, when given in a dissociative dose (4-5 mg/kg IM), renders most patients unconscious and motionless within 5 minutes, while the patient's vital functions are usually maintained. Ketamine's effectiveness as a calming agent is irrespective of the etiology of agitation. Though dissociation often causes hypertension and tachycardia in calm patients undergoing procedural sedation, hyperdynamic vital signs in severely agitated patients will often normalize as ketamine treats its underlying cause, which is uncontrolled psychomotor activity. Dissociative-dose ketamine may be used in the treatment of dangerous agitation caused by head injury, decompensated psychiatric illness, and intoxication with any substance, including PCP, from which ketamine is derived, or even recreational use of ketamine itself, described in an observational cohort of patients with stimulant-induced agitation treated with ketamine.[103]

Ketamine dissociation has been shown to be more effective than alternatives at immediately calming a severely agitated patient, and is supported

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by society guidelines.[102,104-110] Concern regarding ketamine for use as a treatment for agitation centers on its safety. A majority (57%) of patients in an early prehospital study were intubated on arrival to the ED.[111] This result has been demonstrated to be related to circumstances unique to the study site, and subsequent work has shown much lower rates of intubation,[112] though apprehension around the use of ketamine to treat agitation remains. Ketamine has also been implicated in several high-profile prehospital deaths that have animated popular press discussions of excessive force by police.[110,113-116] Because of this scrutiny, it is essential that emergency and prehospital clinicians be expert in the safe use of ketamine as a calming medication.

Because dissociative-dose ketamine has demonstrated high efficacy in quickly calming agitated patients, there is the temptation to use a subdissociative dose, reasoning that smaller doses will be still be effective, but safer. This misunderstands ketamine's dose-response, however, as subdissociative dosing will have an unpredictable effect and could result in partial dissociation or hallucinations with a preserved level of consciousness that may cause the patient to become more agitated. Though there are data suggesting lower doses,[117,118] until literature more robustly elucidates outcomes across the range of doses, when treating dangerously severe agitation, it is prudent to administer a dose that is at least high enough to cause dissociation.

Managing Adverse Effects and Monitoring Response

Though patients in dissociation usually maintain their posture, airway reflexes, ability to manage secretions, and respiratory drive, it is critical that clinicians who administer ketamine understand that any nonintubated patient who receives a dissociative dose of ketamine, for any indication, is at risk for hypoventilation and apnea for the duration of their dissociation. This may occur as the result of malpositioning of the head and neck, laryngospasm, hypersalivation and mishandling of secretions, or central apnea. Dissociated patients therefore require vigilant monitoring for hypoventilation with an airway-capable clinician at bedside or immediately available. Among the minority of patients who develop hypoventilation after a dose of ketamine, most will respond to simple maneuvers such as a head tilt-chin lift, jaw thrust, or a brief period of assisted ventilation; however, intubation will occasionally (and idiosyncratically) be necessary, and emergency clinicians must be prepared to intervene across the spectrum of cardiorespiratory support.

After a severely agitated patient is treated with dissociative-dose ketamine, maintain adequate force as the patient calms; restraints should not be necessary. In minutes, the patient will be still, and the focus of care can pivot from control to resuscitation. Move the patient to the appropriate environment, establish vascular access and cardiorespiratory monitoring, which should include capnography, if providing supplemental oxygen. A careful examination should be directed at the dangerous causes and effects of agitation and should proceed with special attention to core temperature, oxygenation, blood glucose, organ perfusion, and occult trauma.

Future Directions: The Horizon of Ketamine Therapy in Emergency Medicine

Asthma

Ketamine has been studied for decades as a rescue therapy in patients with severe asthma. Early prospective studies demonstrated that a subdissociative dose of ketamine is ineffective for acute asthma.[119,120] Though the literature is replete with case reports demonstrating sudden clinical improvement and prevention of intubation when dissociative dose ketamine was used,[121-124] this benefit has not withstood the scrutiny of prospective study.[86] The mechanism by which ketamine might benefit patients with severe asthma is also uncertain. Although ketamine was thought to have bronchodilatory properties, randomized controlled trial evidence suggests that it is not superior to conventional fentanyl postintubation analgesia;[125] its benefit may arise from reducing the respiratory rate.[126] At present, it is reasonable to administer dissociative-dose ketamine to a patient with severe, treatment-refractory asthma who otherwise will require intubation, especially to facilitate noninvasive positive-pressure ventilation, given the harms of intubation in status asthmaticus. If this strategy is undertaken, a full intubation setup is required, and the clinician should remain at bedside, ready to move forward, until clinical improvement is established or endotracheal intubation is performed.

Status Epilepticus

A wide body of mostly observational and retrospective literature suggests that dissociative-dose ketamine is effective at terminating seizures in treatment-refractory status epilepticus.[127-129] ED literature is confined to a single case report,[130] though it has received attention in the prehospital literature,[131] and registries show that it may have broader application in the ED,[132] perhaps in consultation with admitting teams. Ketamine's most common use in the seizing patient is as a loading dose (eg, 2 mg/kg IV, given over 10-20 minutes in nonintubated patients) and infusion (eg, 5 mg/kg/hr, ideal body weight) when first-, second-, and even third-line anticonvulsant therapies have failed. It may be particularly useful in pediatric patients, in whom propofol infusions are avoided because of the danger of propofol infusion syndrome.

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Weak literature supports the use of dissociative-dose ketamine in status epilepticus patients with ongoing seizures refractory to at least 2 conventional agents, ideally in collaboration with downstream clinicians and continuous electroencephalograph monitoring.

Alcohol Withdrawal Syndrome and Alcohol Use Disorder

Retrospective intensive care unit data support the use of ketamine as an adjunctive agent in the management of alcohol withdrawal syndrome that is resistant to usual therapies such benzodiazepines, phenobarbital, and propofol.[133-135] These data do not presently indicate more than a very limited role for ketamine in the ED management of alcohol withdrawal syndrome; perhaps it is best considered an initial treatment of alcohol withdrawal syndrome-related dangerous agitation, to establish control and facilitate specific alcohol withdrawal syndrome therapies. (See the "Treatment of Agitation" section on page 10.)

Ketamine is also being investigated as an anti-craving treatment for patients with alcohol use disorder.[136] Early studies are promising, including an emergency medicine-relevant protocol that showed 39% absolute improvement in self-reported abstinence after a single 2.5 mg/kg IM dose of ketamine, in combination with psychotherapy.[137] Current ED treatment of alcohol use disorder should focus on appropriate withdrawal management and initiation of the United States Food and Drug Administration (FDA)-approved anti-craving medications, naltrexone or acamprosate, in all willing patients.

Treatment-Resistant Depression

Ketamine has received considerable recent attention as a therapy for treatment-resistant depression. High-level evidence published in high-impact journals[138-140] has fueled great public (and investor) interest and spawned the development of an on-patent intranasal ketamine enantiomer[141] as well as a burgeoning ketamine infusion clinic and telehealth industry that promises relief from depression, anxiety, chronic pain, obsessive-compulsive disorder, posttraumatic stress disorder, and substance use disorders.[142,143] As these outpatient practices grow, emergency clinicians may see referrals for complications and therapeutic misadventures, including adverse effects previously thought to occur only in patients with chronic ketamine abuse, such as cystitis.[144] Of particular therapeutic interest to emergency clinicians is the potential for ketamine to acutely reverse suicidality, supported by 3 early prospective ED-based trials.[145-147] Though presently not ready for ED application outside of formal protocols in collaboration with psychiatry, given the current nationwide shortage of inpatient psychiatry resources, the prospect of treat-and-release of suicidal patients is an exciting development.

Summary

- Dissociative-dose ketamine has a long history of efficacious use in procedural sedation of adults and children in the ED. It has demonstrated safety and efficacy when combined with propofol in the same syringe, but clinicians might achieve better results by dosing the 2 agents independently, as needed to manage the patient's needs.
- Dissociated patients can develop hypoventilation from airway malpositioning, hypersalivation, central apnea, and laryngospasm and require continuous resuscitation-level monitoring with an airway-capable clinician immediately available.
- Partially dissociative doses of ketamine have unpredictable effects. If a subdissociative dose is given for procedural sedation and the patient develops psychiatric distress prior to the procedure, the proper response is to treat with additional ketamine to push the patient into dissociation.
- Psychiatric distress on emergence from ketamine-dissociated procedural sedation can be effectively prevented with pre-induction coaching and analgesia, and can be treated with a titratable conventional sedative (eg, midazolam or propofol).

5 Things That Will Change Your Practice

1. Propofol is an effective treatment for several common problems that arise during ketamine-based procedural sedation: hypertension, rigidity, and psychiatric distress.
2. Ketamine is more likely to deliver effective analgesia without psychoperceptual adverse effects if it is administered slowly.
3. Dissociative-dose ketamine is the most effective treatment for dangerously severe agitation, but routine agitation is better treated with conventional titratable sedatives, such as midazolam or droperidol.
4. In RSI, ketamine is not contraindicated in patients with increased intracranial pressure, and it is much less likely to cause hypotension than propofol.
5. DSI is the administration of dissociative-dose ketamine without a paralytic in a patient who does not otherwise tolerate preoxygenation or preparation for intubation. It is followed later by administration of a paralytic and laryngoscopy. This technique may offer a significant safety benefit compared to performing RSI on a patient who is inadequately preoxygenated or when the team is otherwise not fully prepared to intubate.

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Case Conclusions

CASE 1

For the 43-year-old man who developed psychiatric distress after being given 40 mg IV ketamine for a fracture reduction…

You administered an additional 40 mg IV ketamine, the patient became dissociated and calm, and the procedure was carried out uneventfully. It is commonly believed that since a dissociative dose causes complete dissociation, for less painful or briefer procedures, a subdissociative dose may be beneficial. However, ketamine is not titratable in this way, and this strategy may result in partial dissociation, where the patient experiences distressing perceptual disturbance that can cause severe agitation. In this case, because this occurred before the procedure began (ie, on induction), the correct treatment was to push the patient to full dissociation with more ketamine.

CASE 2

For the 22-year-old man who was thrown from his motorcycle, suffering head injury…

You chose ketamine for induction because it preserves or augments blood pressure, which is vital in this patient with likely brain injury and severe hemorrhage from pelvic injury. It was commonly stipulated that ketamine is contraindicated in patients who have brain injury, for concern that it could increase intracranial pressure. However, more recent evidence[74] demonstrates increased intracranial pressure resulting from ketamine is not clinically significant and that a vasodilatory effect may improve overall cerebral perfusion. Avoiding hypotension is a crucial goal in resuscitation of the brain-injured patient; ketamine is therefore an excellent choice as an induction agent.

CASE 3

For the 74-year-old woman with hematemesis from metastatic pancreatic cancer…

Recognizing that it would be difficult to titrate opioids to high enough doses to be effective in a relevant time frame, you elected to treat her pain with analgesic-dose ketamine. You administered 0.3 mg/kg IV over 20 minutes, and then started infusion at 0.3 mg/kg/hr. She became much more comfortable, but then a bit loopy and confused, so you decreased the dose to 0.2 mg/kg/hr. On reassessment, her mental status had returned to normal, and she gratefully told you that this was the first time in months that she had been without pain. She died the following day.

- Analgesic-dose ketamine is best delivered slowly, which minimizes psychoperceptual effects. This can be accomplished with administration via IV piggyback, infusion, intranasal, IM, nebulized, transmucosal, or oral routes.
- Dissociative-dose ketamine is the most effective treatment for agitation, but it is favored over conventional sedatives only for patients who are uncontrollably violent or patients who are too agitated to allow management of an immediately dangerous condition.
- In airway management, ketamine can be administered several minutes before paralytic administration to facilitate preoxygenation or preparation (DSI).
- For patients with expected high anatomic airway difficulty, or when even a brief period of apnea is dangerous, ketamine can be used to intubate without a paralytic (KOBI).
- There is mixed evidence regarding ketamine's use in patients with severe asthma, but it may be reasonable to administer it to a patient with severe, treatment-refractory asthma who will otherwise require intubation.
- Ketamine can be effectively used as an adjunct to conventional therapies in treatment-refractory status epilepticus and alcohol withdrawal.
- Ketamine has emerging indications as a treatment for depression and relief of acute suicidality.
- Chronic ketamine use and addiction can cause severe damage to the urological system.

Time- and Cost-Effective Strategies

- Establish a protocol for analgesic-dose ketamine that includes a weight-based loading dose over 10 to 20 minutes, followed by an option for a continuous infusion that is titrated to relief of pain with preservation of a calm affect.
- Assemble an "agitated patient kit" containing all the materials and medications required to treat severe agitation, such as a ketamine vial adequate for IM dosing, syringe, draw and IM injection needles, and an alcohol swab, and establish a protocol to quickly obtain ketamine at an adequate concentration for IM usage. Because IM ketamine is less potent than IV, usual dosing is 300 to 500 mg IM, and is best administered using

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Risk Management Pitfalls in Using Ketamine in the Emergency Department

1. **"We didn't closely monitor the patient because ketamine is so safe."** Any patient who is dissociated with ketamine and not already intubated is at risk for hypoventilation and apnea from a variety of mechanisms and requires full resuscitation-level monitoring, with careful attention to ventilation and an airway-capable clinician immediately available for the duration of dissociation.

2. **"We added high doses of fentanyl to ketamine during procedural sedation because we were performing a very painful procedure."** Ketamine is a very powerful analgesic, and dissociated patients feel no pain or any other external stimuli. Adding fentanyl to ketamine in procedural sedation confers risk without significant benefit.

3. **"We bagged the patient aggressively; this is supposed to break laryngospasm."** Simple maneuvers such as a head tilt/chin lift and jaw thrust are usually adequate to manage the rare of occurrence of laryngospasm. If ineffective, almost all patients will be successfully treated with gentle bag-mask ventilation. It may be possible, though rare, for patients who develop apnea related to muscle rigidity and/or laryngospasm to require paralysis and intubation to restore ventilation.

4. **"We used propofol for RSI induction because ketamine is contraindicated in head trauma patients."** Ketamine does not meaningfully increase intracranial pressure and, unlike propofol, maintains blood pressure–a critical goal in neuro-resuscitation.

5. **"After usual asthma therapies failed, we used ketamine as a recommended treatment for severe asthma. We didn't expect the patient to decompensate."** Clinicians must have full RSI setup in place prior to dissociating a severe asthma patient with ketamine. Some patients with severe asthma will not respond to ketamine and will require endotracheal intubation.

6. **"We knew laryngoscopy was likely to fail, but we performed RSI because we didn't have the equipment needed to do an awake intubation."** Much of the safety of a conventional topicalized awake intubation can be achieved with KOBI (dissociative-dose ketamine without a paralytic), to keep the patient breathing during airway management.

7. **"We gave large doses of midazolam, but couldn't calm the patient in time to prevent a bad outcome."** Dissociative-dose ketamine is the best agent to calm the uncontrollably violent patient, especially patients who are resistant to alternative treatments. Once a dissociative dose of ketamine is administered, the patient requires continuous resuscitation-level monitoring for the duration of dissociation.

8. **"The patient had a Glasgow Coma Scale score of 3 after EMS gave a big dose of ketamine for agitation, so he required intubation."** Most patients treated for agitation with dissociative-dose ketamine will emerge from dissociation safely and not require intubation; however, preparation for intubation and vigilant monitoring of ventilation for the duration of dissociation is required.

9. **"The patient had a history of opioid use disorder and asked us not to use opioids, but we didn't have any choice, because he had such severe pain."** Analgesic-dose ketamine is effective for severe pain and is an appropriate choice either as a first-line analgesic agent or when opioids are ineffective or undesired.

10. **"Ketamine is recommended for alcohol withdrawal syndrome, and it seemed to quiet the patient."** Ketamine should be used as an adjunct in severe alcohol withdrawal syndrome only in combination with adequate doses of GABAergic agents such as benzodiazepines or barbiturates.

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ketamine at a concentration of 100 mg/mL.
- Use a procedural sedation checklist to assist clinicians in preprocedural evaluation and preparation, including airway supplies and recommending dosing strategies.

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Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the author, are noted by an asterisk (*) next to the number of the reference.

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CME Questions

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1. What is a reasonable intravenous (IV) analgesic dose of ketamine for a healthy, normal-sized adult?
a. 0.3 mg/kg
b. 1 mg/kg
c. 3 mg/kg
d. 10 mg/kg

2. Compared with quick IV bolus administration of analgesic-dose ketamine, what is a benefit of slowing the administration rate?
a. Fewer allergic reactions
b. Less hypotension
c. Diminished psychoperceptual effects
d. Decreased telemetry monitoring requirement

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3. **A 29-year-old man received 1 mg/kg IV ketamine for procedural sedation. As he is recovering after the procedure, he develops agitation and psychiatric distress. What is the best treatment for this patient?**
   a. Additional ketamine
   b. Diphenhydramine
   c. Midazolam
   d. Do nothing and observe

4. **A 51-year-old woman is given 0.5 mg/kg IV ketamine to facilitate abscess drainage. Two minutes after administration, she begins screaming violently, in extreme emotional distress. The procedure has not yet begun. What is the best next step?**
   a. Administer diphenhydramine
   b. Administer more ketamine
   c. Administer succinylcholine and intubate
   d. Call off the procedure

5. **When used for procedural sedation, what is the usual effect of ketamine on heart rate and blood pressure?**
   a. No effect on heart rate or blood pressure
   b. Increase in heart rate, decrease in blood pressure
   c. Decrease in heart rate, increase in blood pressure
   d. Increase in heart rate, increase in blood pressure

6. **What is a potentially dangerous consequence of administering a dissociative dose of ketamine?**
   a. Bradycardia
   b. Hypoventilation
   c. Angioedema
   d. Hypothermia

7. **A 6-year-old boy is given 1.5 mg/kg IV ketamine for procedural sedation for a fracture reduction. Several minutes later, his respirations become noisy and partially obstructed. His head is repositioned without effect, but improvement is noted after a jaw thrust. What is a potential cause of his partial airway obstruction?**
   a. Foreign body
   b. Angioedema
   c. Bronchospasm
   d. Laryngospasm

8. **A 61-year-old man with many chronic obstructive pulmonary disease admissions presents by EMS hypoxic, in respiratory distress. He requires intubation but is too agitated to allow for safe preoxygenation, so a dissociative dose of ketamine is given, which calms him. He then tolerates noninvasive ventilation, as the team prepares for intubation. 100 mg IV rocuronium is given, and the patient is intubated uneventfully. What is this technique?**
   a. Rapid sequence intubation
   b. Ketamine-only breathing intubation
   c. Delayed sequence intubation
   d. Topicalized awake intubation

9. **An alcohol-intoxicated patient is brought to the emergency department by EMS. He is mildly agitated but redirectable when engaged and is able to participate in history-gathering, but requires a calming medication to prevent elopement. Which is the most appropriate agent to use for this patient?**
   a. Droperidol
   b. Diphenhydramine
   c. Ketamine
   d. Propofol

10. **A 90-kg man intoxicated with phencyclidine presents to the ED after being assaulted with a knife and baseball bat. He is critically injured but combative, and resists all treatments. No IV access has been established. What is the most appropriate initial pharmacologic management for this patient?**
    a. Administer lorazepam 2 mg orally
    b. Administer ketamine 50 mg intramuscularly (IM)
    c. Administer succinylcholine 100 mg IM
    d. Administer ketamine 450 mg IM

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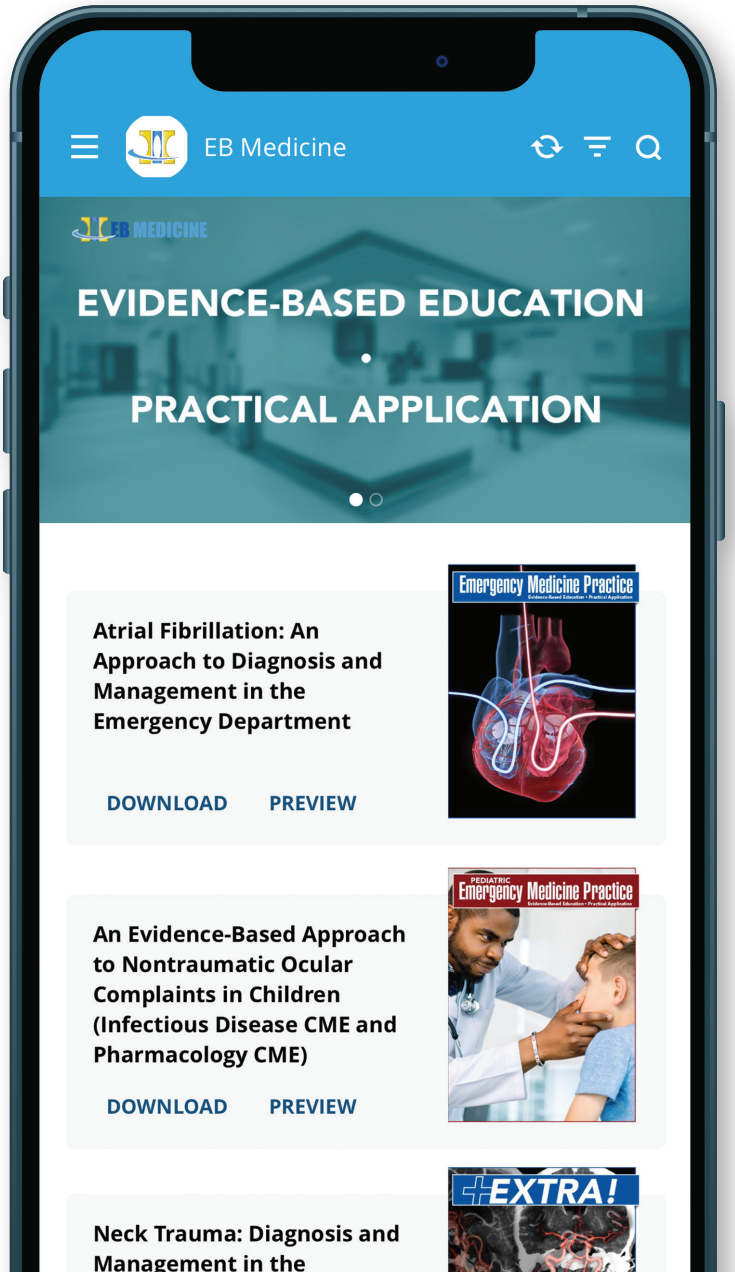

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Points & Pearls

MAY 2024 | VOLUME 26 | ISSUE 5

Current Concepts in Ketamine Therapy in the Emergency Department

Points

Procedural Sedation and Anesthesia (PSA)

- Dissociative-dose ketamine is often superior to alternative agents for PSA, as the patient is completely unaware of painful stimuli while airway, breathing, and circulation are usually maintained.
- Ketamine can cause hypertension, muscle rigidity, and psychiatric distress during PSA; these adverse effects are usually effectively treated with small doses of propofol or midazolam as needed.
- A patient who develops agitation shortly after induction during ketamine PSA is likely partially dissociated because they were under-dosed.
- Psychiatric distress on emergence from ketamine PSA is less likely if the patient receives adequate analgesia prior, is coached on the anticipated effects, and emerges in a quiet environment.

Analgesia

- Ketamine is safe and effective for analgesia in low dose (0.1-0.3 mg/kg IV), and can be used either as a first-line agent or when alternatives such as opioids are ineffective or undesired. Continuous monitoring of vital signs is not necessary.

Airway Management

- Ketamine has advantages over alternatives when used as an induction agent in RSI, including stimulation of cardiorespiratory tone and analgesia that outlasts its dissociative effects.
- For patients whose agitation prevents optimal preoxygenation or preparation for intubation, delayed sequence intubation can be used by administering ketamine in a dissociative dose some time prior to the paralytic.

Agitation

- Ketamine is the most effective treatment for severe agitation but should not be used in mild or moderate agitation because it is not titratable and requires critical care resources during the period of dissociation.

Asthma

- Ketamine may be effective in preventing intubation in treatment-refractory asthma, but it should accompany preparations to intubate, with vigilant monitoring for response to therapy.

Alcohol Use Disorder

- Early evidence suggests a possible role for ketamine as an adjunctive agent in treatment of severe alcohol withdrawal and may have anti-craving properties to address the underlying use disorder.

Status Epilepticus

- ICU data demonstrate efficacy in using ketamine for status epilepticus that has not responded to first- and second-line anticonvulsants.

Depression and Suicidality

- Emerging evidence suggests ketamine is effective in treatment of refractory depression and suicidality. A variety of protocols are used in diverse treatment settings.
- Chronic recreational or therapeutic use of ketamine can lead to cystitis and cholangiopathy.

Pearls

- A patient receiving a dissociative dose of ketamine who is not already intubated may develop hypoventilation and requires continuous resuscitation-level monitoring.
- Partial dissociation causing psychiatric distress should be treated with additional ketamine at the outset of the procedure, or with titratable conventional sedatives (eg, midazolam).
- When using ketamine for analgesia, slow delivery via infusion, intranasal, IM, or nebulized administration reduces the intensity of psychoperceptual effects.
- Ketamine is not contraindicated in patients with increased intracranial pressure and may be preferable for use in the airway management of brain-injured patients because of its relative preservation of blood pressure.
- When it is desired to maintain breathing during intubation, but performing a conventional topicalized awake approach is difficult to execute, a similar degree of safety can be achieved using ketamine without a paralytic to facilitate laryngoscopy. **(See Figure 2.)**
- Ketamine can be used in the agitated, potentially seriously injured patient instead of intubation. If imaging clears the patient of dangerous injury, the patient may be spared the need for intubation. **(See Figure 3.)**

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